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| APPLICATION NO. | FILING DATE | FIRST NAMED INVENTOR | ATTORNEY DOCKET NO. | CONFIRMATION NO. |
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| 10/732,862 | 12/10/2003 | Katelynne Lyons | ICC-136.0 (4564/88881) | 9117 |

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| MCGAW, MICHAEL M | |

| ART UNIT | PAPER NUMBER |
|---|---|
| 1648 | |

DATE MAILED: 12/17/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

| Office Action Summary | Application No. | Applicant(s) | |
|---|---|---|---|
| | 10/732,862 | LYONS ET AL. | |
| | Examiner | Art Unit | |
| | Michael M. McGaw | 1648 | |

*-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --*

**Period for Reply**

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

**Status**

1)☒ Responsive to communication(s) filed on *29 March 2004*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

**Disposition of Claims**

4)☒ Claim(s) *1-46* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-46* is/are rejected.

7)☒ Claim(s) *1,11 and 25* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

**Application Papers**

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

**Priority under 35 U.S.C. § 119**

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

**Attachment(s)**

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

## DETAILED ACTION

### *Priority*

It is noted that this application appears to claim subject matter disclosed in prior Application No. 10/080,299 and 10/082,014, filed Feb. 21, 2002. A reference to the prior application must be inserted as the first sentence of the specification of this application or in an application data sheet (37 CFR 1.76), if applicant intends to rely on the filing date of the prior application under 35 U.S.C. 119(e) or 120. See 37 CFR 1.78(a). For benefit claims under 35 U.S.C. 120, the reference must include the relationship (i.e., continuation, divisional, or continuation-in-part) of all nonprovisional applications. Also, the current status of all nonprovisional parent applications referenced should be included. *Most particularly, the status of the applications should be updated, as it appears that they have been expressly abandoned.*

If the application is a utility or plant application filed under 35 U.S.C. 111(a) on or after November 29, 2000, the specific reference to the prior application must be submitted during the pendency of the application and within the later of four months from the actual filing date of the application or sixteen months from the filing date of the prior application. If the application is a utility or plant application which entered the national stage from an international application filed on or after November 29, 2000, after compliance with 35 U.S.C. 371, the specific reference must be submitted during the pendency of the application and within the later of four months from the date on which the national stage commenced under 35 U.S.C. 371(b) or (f) or sixteen months from the filing date of the prior application. See 37 CFR 1.78(a)(2)(ii) and (a)(5)(ii). This

time period is not extendable and a failure to submit the reference required by 35 U.S.C. 119(e) and/or 120, where applicable, within this time period is considered a waiver of any benefit of such prior application(s) under 35 U.S.C. 119(e), 120, 121 and 365(c). A priority claim filed after the required time period may be accepted if it is accompanied by a grantable petition to accept an unintentionally delayed claim for priority under 35 U.S.C. 119(e), 120, 121 and 365(c). The petition must be accompanied by (1) the reference required by 35 U.S.C. 120 or 119(e) and 37 CFR 1.78(a)(2) or (a)(5) to the prior application (unless previously submitted), (2) a surcharge under 37 CFR 1.17(t), and (3) a statement that the entire delay between the date the claim was due under 37 CFR 1.78(a)(2) or (a)(5) and the date the claim was filed was unintentional. The Director may require additional information where there is a question whether the delay was unintentional. The petition should be addressed to: Mail Stop Petition, Commissioner for Patents, P.O. Box 1450, Alexandria, Virginia 22313-1450.

### *Specification*

The lengthy specification has not been checked to the extent necessary to determine the presence of all possible minor errors. Applicant's cooperation is requested in correcting any errors of which applicant may become aware in the specification.

### *Claim Objections*

Claims 1, 11, 25 are objected to because of the following informalities: Where a claim sets forth a plurality of elements or steps, each element or step of the claim

should be separated by a line indentation. 37 CFR 1.75(i). There may be plural indentations to further segregate subcombinations or related steps. See MPEP 608.01(m). It is noted that the claims contain numerous different elements and subcombinations. For example, claim 1, part (b) contains the combinations (i)-(iii) which are not separated but rather are embedded within (b). Appropriate correction is required.

***Claim Rejections - 35 USC § 112, ¶2***

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

The claim(s) are replete with indefinite and functional or operational language. The structure which goes to make up the device must be clearly and positively specified. The structure must be organized and correlated in such a manner as to present a complete operative device. The claim(s) must be in one sentence form only. Note the format of the claims in the U.S. Publication No. 2004/0054139 A1 to Page at al. Appropriate correction is required.

Claims 1-46 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

1. Claims 1, 11 and 25 contain many ambiguities making meaningful interpretation difficult at best. The wording of the claims, including the grammatical structure and most importantly the liberal usage of 'or' within the claims, renders them subject to numerous

possibilities in their application. All claims directly or indirectly refer to claims 1, 11 and 25. Appropriate correction is required.

2. Part (b)(i) of claim 1 is virtually undecipherable. First it states "zero to all residues in a sequence in said HBc immunodominant loop are present or replaced and peptide-bonded..." It does not make sense to say zero residues are present. Moreover, if no residues are present then what is peptide-bonded to the one to about 245 amino acids? Because there is an "or" between present or replaced, can some residues be present and some residues be replaced? Further along in part (i) more options are possible based upon the liberal use of "or" within the claim. It is not clear to what the parts following the "or" in the phrase "or a sequence of up to..." and "or a chemically-reactive linker..." are an alternative. Is it an alternative to the entire part beginning at "zero to all..." or an alternative to the part "one to about 245 amino acid residues..."? Appropriate correction is required.

3. Applicant uses the word "optionally" in part (b) of claim 1 and 11. In reading the sentence it looks, at first glance, as though all of part (b) is optional. What is optional in the sentence? The claim is being interpreted as though the only optional part is the part between the (b) and the (i). Appropriate correction is required.

4. Claim 1, part (b) states "between residue positions about 76 through about 85 (in the immunodominant loop)..." Such a phrase does not define the boundaries of the immunodominant loop but merely tells one that these residues are within the immunodominant loop. Consequently, when it is stated two lines later "in said immunodominant loop", there exists a lack of antecedent basis. Thus all subsequent

claims using this term also lack antecedent basis for the term. See for instance claim 11. Appropriate correction is required.

5. Applicant uses the phrase "substituted" in claims 1, 11 and 25. Applicant does not specifically define what is meant by substituted. Additionally, Applicant provides inconsistent definitions for the term "conservatively substituted in the specification. The definition on page 25 states "[t]he term 'conservative substitution' as used herein denotes that one amino acid residue has been replaced by another, biologically similar residue." It is not exactly clear what applicant means by biologically similar, though the subsequent examples do provide some guidance. Then on page applicant tells us:

> Where a HBc sequence is truncated at the C-terminus beyond position 163 or at the N-terminus, or contains one or more deletions in the immunogenic loop, the number of substituted residues is proportionally different because the total length of the sequence is less that 163 residues. ***Deletions elsewhere in the molecule are considered conservative substitutions for purposes of calculation.*** (emphasis added)

To say that a deletion is a conservative substitution is not consistent with the prior definition requiring that one amino acid is replaced by another, biologically similar residue.

It is also not clear as to which sequence one compares to determine a conservative substitution. A generic HBc sequence is about 185 residues in length. On page 74 of the specification applicant discusses numerous sequences. It appears that the preferred sequence is that of subtype *ayw* from positions 1 to 149, but the applicant in no way limits himself to that sequence. Furthermore, applicant makes even this more vague when he indicates that this will be less any truncation due to terminal deletions. To then provide that portions of different sequences from different mammalian HBc

proteins may be used really makes the issue hopelessly muddied. Appropriate correction is required.

6. In claim 25, under the section directed at Domain IV, it is indicated that the molecule contains fewer than about ten arginine, lysine residues or mixtures of both resides. First, it indicates that it can contain mixtures of both residues but the statement is ambiguous as to how many of each. If it contains a mixture of both could it have a mixture of nine arginine residues and nine lysine residues or can the total of the residues not exceed nine? Appropriate correction is required.

Second, if it contains, for example, nine arginine residues then it would not be "substantially free of binding to nucleic acid" as required later in the claim. Thus, this limitation is incompatible with the later claim language. Appropriate correction is required.

7. The term "substantially" in claims 1 and 25 is a relative term that renders the claim indefinite. The term " substantially" is not defined by the claim, the specification does not provide a standard for ascertaining the requisite degree, and one of ordinary skill in the art would not be reasonably apprised of the scope of the invention. The specification provides:

> The substantial freedom of nucleic acid binding exhibited by contemplated particles can be readily determined by a comparison of the absorbance of the particles in aqueous solution measured at both 280 and 260 nm; i.e., a 280/260 absorbance ratio. The contemplated particles do not bind substantially to nucleic acids that are oligomeric and/or polymeric DNA and RNA species originally present in the cells of the organism used to express the protein. Such nucleic acids exhibit an absorbance at 260 nm and relatively less absorbance at 280 nm, whereas a protein such as a contemplated chimer absorbs relatively less at 260 nm and has a greater absorbance at 280 nm.

That the substantial freedom can be determined does not help when one does not know the parameters. The specification then goes on to discuss particles "sufficiently free" of binding, which is not the same thing as "substantially free" of binding. Moreover, even the explanation of sufficiently free of binding does not provide the requisite degree to aid in understating the scope of Applicant's claim.

8. The term "more stable" in claim 25 is a relative term that renders the claim indefinite. The term "more stable" is not defined by the claim, the specification does not provide a standard for ascertaining the requisite degree, and one of ordinary skill in the art would not be reasonably apprised of the scope of the invention. The Examiner cannot find in the specification exactly how on determines that a molecule is more stable than an otherwise identical molecule as specified I the functional language of the claim.

9. The terms "of at least about" and/or "up to about" in claims 1, 11 and 25 are relative terms which render the claim indefinite. These terms are not defined by the claim, the specification does not provide a standard for ascertaining the requisite degree, and one of ordinary skill in the art would not be reasonably appraised of the scope of the invention. Appropriate correction is required.

10. Claim 25 states "Domain III is an HBC sequence from position 86 through position 135 peptide-bonded to residue 85..." Thus, residue 85 must be present. In a prior part of the claim referring to Domain II it is stated that zero to all residues of HBc positions are present or are replaced and peptide bonded to one to about 75 amino acid residues that are heterologous... Thus, the later part would indicate that residue 85

must be present and Domain III is peptide bonded to residue 85 of Domain II. The earlier part indicates that residue 85 may or may not be present, it may be replaced and it may be peptide bonded to a heterologous epitope. Clearly, this is a situation where the liberal use of alternatives created by the claim language results in fatal inconsistencies within the claim. Appropriate correction is required.

### *Claim Rejections - 35 USC § 112, ¶1*

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-46 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. This rejection is made concurrently with the rejection below.

Claims 1-46 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

The factors to be considered in determining whether a disclosure meets the enablement requirements of 35 U.S.C. 112, first paragraph, have been described in *In re Wands*, 858 F.2d 731, 8 USPQ2d 1400 (Fed. Cir., 1988). The court in Wands states, "Enablement is not precluded by the necessity for some experimentation, such as routine screening. However, experimentation needed to practice the invention must not be undue experimentation. The key word is 'undue', not 'experimentation'" (Wands, 8 USPQ2sd 1404). Clearly, enablement of a claimed invention cannot be predicated on the basis of quantity of experimentation required to make or use the invention. "Whether undue experimentation is needed is not a single, simple factual determination, but rather is a conclusion reached by weighing many factual considerations" (Wands, 8 USPQ2d 1404). Among these factors are: (1) the nature of the invention; (2) the state of the prior art; (3) the relative skill of those in the art; (4) the predictability or unpredictability of the art; (5) the breadth of the claims; (6) the amount of direction or guidance presented; (7) the presence or absence of working examples; and (8) the quantity of experimentation necessary.

Claims 1 and 11 specify a chimer molecule with up to about 20 percent substituted amino acid residues in the HBc sequence. Claim 25 specifies a chimer molecule with up to about 10 percent substituted amino acid residues in the HBc sequence. With 20 percent substituted amino acid residues Applicant is specifying a molecule with up to 30 amino acid substitutions variously arranged along the sequence. While the Examiner does not have a specific number, it seems reasonable to conclude that this would greatly exceed many millions of possible permutations. Based upon

Applicant's disclosure it appears that Applicant was not in possession of even a small fraction of such molecules. More importantly, Applicant fails to provide necessary guidance that would lead one to such molecules. First note, it is stated substituted and not conservatively substituted. Therefore, it seems more than reasonable to assume that a nonconservative substitution in the amino acid sequence will have a deleterious effect on the conformation of the HBc molecule. Second, even a single substitution can have an unpredictable effect on conformation of the resulting molecule. "The significance of particular amino acids and sequences for different aspects of biological activity cannot be predicted a priori but must be determined from case to case by painstaking experimental study." See Rudinger, J. at page 6. Thus, a single amino acid, let alone 30 amino acids can create problems in conformation that can't be adequately predicted in advance. Moreover, as mentioned above Applicant has failed to describe that to which one compares in making the determination; does one compare sequence *ayw* or which sequence in particular?

Considering the state of the art as discussed above and the high unpredictability and the lack of guidance provided in the specification, one of ordinary skill in the art would be burdened with undue experimentation to construct a chimer molecule containing up to 20%, or even 10%, substituted amino acid residues.

***Claim Rejections - 35 USC § 102***

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless –

(a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 1, 3, 8-14, 23-28, 40-42 and 46 are rejected under 35 U.S.C. 102(b) as being anticipated by Zlotnick, et al. (1997).

In claim 1 Applicant claims "A recombinant chimer hepatitis B core (HBc) protein molecule up to about 600 amino acid residues in length that (a) contains an HBc sequence of at least about 125 of the N-terminal 183 amino acid residues of the HBc molecule that includes the HBc sequence of residue positions 4 through about 75 and about 85 through about 140 in which one or both cysteine residues at positions 48 and 107 is replaced by another residue; (b) optionally contains a peptide-bonded heterologous amino acid residue sequence at one or more of the N-terminus, between residue positions about 76 through about 85 (in the HBc immunodominant loop) or the C-terminus of the chimer, and wherein (i) zero to all residues in a sequence in said HBc immunodominant loop are present or replaced and peptide-bonded to one to about 245 amino acid residues of said heterologous amino acid residue sequence that constitutes an immunogen or a sequence of up to about 40 residues that constitutes an anti-antigen or a chemically-reactive linker residue for a conjugated hapten or (ii) the sequence of HBc at positions 76 through 85 is present and free from deletions and heterologous residues or (iii) one or more of residues 76 through 85 is absent or replaced, (c) contains one or both of (i) one to three cysteine residues at an amino acid position of the chimer molecule corresponding to amino acid position -20 to about +1 from the N-

terminus of the HBc sequence of SEQ ID NO:1 [N-terminal cysteine residue(s)] in a sequence other than that of the HBc precore sequence and (ii) one to three cysteine residues toward the C-terminus of the molecule from the C-terminal residue of the HBC sequence and within about 30 residues from the C-terminus of the chimer molecule [C-terminal cysteine residue(s)]; said chimer molecule (i) containing up to about 20 percent substituted amino acid residues in the HBc sequence, (ii) self-assembling into particles that are substantially free of binding to nucleic acids after expression.

Zlotnick teaches a recombinant chimer hepatitis B core (HBc) protein molecule up to about 600 amino acid residues in length that (a) contains an HBc sequence of at least about 125 of the N-terminal 183 amino acid residues of the HBc molecule that includes the HBc sequence of residue positions 4 through about 75 and about 85 through about 140 in which one or both cysteine residues at positions 48 and 107 is replaced by another residue *(see page 9556, column 2, 2nd full paragraph)*; (b) optionally contains a peptide-bonded heterologous amino acid residue sequence at one or more of the N-terminus, between residue positions about 76 through about 85 (in the HBc immunodominant loop) or the C-terminus of the chimer, and wherein (ii) the sequence of HBc at positions 76 through 85 is present and free from deletions and heterologous residues, (c) contains one or both of (i) one to three cysteine residues at an amino acid position of the chimer molecule corresponding to amino acid position -20 to about +1 from the N-terminus of the HBc sequence of SEQ ID NO:1 [N-terminal cysteine residue(s)] in a sequence other than that of the HBc precore sequence and (ii) one to three cysteine residues toward the C-terminus of the molecule from the C-

terminal residue of the HBC sequence and within about 30 residues from the C-terminus of the chimer molecule [C-terminal cysteine residue(s)] *(see page 9556, column 2, 2nd full paragraph)*; said chimer molecule (i) containing up to about 20 percent substituted amino acid residues in the HBc sequence, (ii) self-assembling into particles that are substantially free of binding to nucleic acids after expression *(see page 9558, column 1, 1st full paragraph and page 9560, column 2, 2nd full paragraph)*. Applicant identifies cysteine residues as present a position 48 and 107 while Zlotnick teaches the cysteine resides as being at positions 48 and 108 (see page 9556, column 2, 2nd full paragraph). It is asserted that Applicant's cysteine residue 107 is Zlotnick's cysteine residue 108 based upon the conserved nature of the hepatitis B core sequence.

In claim 11 Applicant claims "a recombinant chimer hepatitis B core (HBc) protein molecule up to about 380 amino acid residues in length that (a) contains an HBc sequence of at least about 125 of the N-terminal 163 amino acid residues of the HBc molecule that includes the HBc sequence of residue positions 4 through about 75 and about 85 through about 140 in which one or both cysteine residues at positions 48 and 107 is replaced by another residue; (b) optionally includes one or more of the following: (i) a peptide-bonded heterologous sequence of up to about 75 residues at one or more of the N-terminus, in the HBc immunodominant loop and at the C-terminus of the chimer wherein that C-terminal sequence is other than that of HBc from position 163 through the native HBc C-terminus, (ii) zero to all of the residues of the sequence of position

about 76 through about 85 present or replaced and peptide-bonded to said heterologous sequence of up to about 75 amino acid residues that constitute an immunogen, or a sequence of one to about 40 amino acid residues that constitute an anti-antigen or a chemically-reactive linker residue for a conjugated hapten, or the sequence of HBc at position about 76 through about 85 is present and free from deletions and heterologous residues, or one or more of residues about 76 through about 85 is absent or replaced; (c) contains one to three cysteine residues present (i) at an amino acid position of the chimer molecule corresponding to amino acid position -20 to about +1 from the N-terminus of the HBc sequence of SEQ ID NO:1 [N-terminal cysteine residue(s)] in a sequence other than that of the HBc precore sequence, or (ii) toward the C-terminus of the molecule from the C-terminal residue of the HBc sequence and within about 30 residues from the C-terminus of the chimer molecule [C-terminal cysteine residue(s)], or at both locations (i) and (ii); (d) contains up to about 20 percent substituted amino acid residues in the HBc sequence, and (e) self-assembles into particles after expression that upon collection, purification and dissolution, exhibit a ratio of absorbance at 280 nm to 260 nm of 0.9 to about 1.7. "

Zlotnick teaches a recombinant chimer hepatitis B core (HBc) protein molecule up to about 380 amino acid residues in length that (a) contains an HBc sequence of at least about 125 of the N-terminal 163 amino acid residues of the HBc molecule that includes the HBc sequence of residue positions 4 through about 75 and about 85 through about 140 in which one or both cysteine residues at positions 48 and 107 is replaced by another residue; (b) **optionally** includes one or more of the following: (i) a

peptide-bonded heterologous sequence of up to about 75 residues at one or more of the N-terminus, in the HBc immunodominant loop and at the C-terminus of the chimer wherein that C-terminal sequence is other than that of HBc from position 163 through the native HBc C-terminus, (ii) zero to all of the residues of the sequence of position about 76 through about 85 present or replaced and peptide-bonded to said heterologous sequence of up to about 75 amino acid residues that constitute an immunogen, or a sequence of one to about 40 amino acid residues that constitute an anti-antigen or a chemically-reactive linker residue for a conjugated hapten, or the sequence of HBc at position about 76 through about 85 is present and free from deletions and heterologous residues, or one or more of residues about 76 through about 85 is absent or replaced; (c) contains one to three cysteine residues present (i) at an amino acid position of the chimer molecule corresponding to amino acid position -20 to about +1 from the N-terminus of the HBc sequence of SEQ ID NO:1 [N-terminal cysteine residue(s)] in a sequence other than that of the HBc precore sequence, or (ii) toward the C-terminus of the molecule from the C-terminal residue of the HBc sequence and within about 30 residues from the C-terminus of the chimer molecule [C-terminal cysteine residue(s)], or at both locations (i) and (ii); (d) contains up to about 20 percent substituted amino acid residues in the HBc sequence, and (e) self-assembles into particles after expression that upon collection, purification and dissolution, exhibit a ratio of absorbance at 280 nm to 260 nm of 0.9 to about 1.7. Applicant indicates on page 49 of the specification that the absorbance ratio is a function of the deletion of the C-terminal sequence resulting in a core protein that no longer binds nucleic acid. Further,

it is stated that a core particle that has a native sequence that ends at about position 140 to 149 exhibits an absorbance ratio of about 1.7. As Zlotnick's particle had a deletion of the native core sequence up to position 149 and was reported as not binding RNA it is reasonable to conclude that this limitation is clearly met by Zlotnick's core particle.

In claim 25 Applicant claims "[a] recombinant hepatitis B virus core (HBc) protein chimer molecule that has a length of about 135 to about 365 amino acid residues and contains four peptide-linked amino acid residue sequence domains from the N-terminus that are denominated Domains I, II, III and IV, wherein Domain I comprises about 72 to about 150 amino acid residues whose sequence includes: (i) at least the sequence of the residues of position 4 through position 75 of HBc, (ii) the substitution of another residue for the cysteine residue at position 48, (iii) zero to three cysteine residues at an amino acid position of the chimer molecule corresponding to amino acid position -20 to about +1 from the N-terminus of the HBc sequence of SEQ ID NO:1 [N-terminal cysteine residue(s)] in a sequence other than that of the HBc precore sequence, and (iv) an optional immunogenic epitope sequence containing up to about 75 amino acid residues peptide-bonded to one of HBc residues 2-4; Domain II comprises up to about 85 amino acid residues peptide-bonded to HBc residue 75 of Domain I in which (i) zero to all residues in the sequence of HBc positions 76 through 85 are present or replaced and peptide-bonded to one to about 75 amino acid residues that are heterologous to the HBc loop and constitute an immunogen, or a sequence of one to about 40 amino acid

residues that constitute an anti-antigen or a chemically-reactive linker residue for a conjugated hapten, or (ii) the sequence of HBc at positions 76 through 85 is present and free from deletions or added heterologous residues; Domain III comprises an HBc sequence from position 86 through position 135 peptide-bonded to residue 85 of Domain II in which another residue is substituted for the cysteine of position 107; Domain IV comprises: (i) five through about thirty residues of an HBc amino acid residue sequence from position 136 through about 165 peptide-bonded to the residue of position 135 of Domain III, (ii) zero to three cysteine residues [C-terminal cysteine residue(s)] within about 30 residues from the C-terminus of the chimer molecule, (iii) zero to about 75 amino acid residues in a sequence other than that present in HBc from position 165 to the C-terminus, and the sequence of the chimer molecule from HBc position 150 through the C-terminus of the chimer molecule containing fewer than about ten arginine, lysine residues or mixtures of both residues; said chimer molecule (i) having an amino acid residue sequence in which up to about 10 percent of the amino acid residues are substituted in the HBc sequence of the chimer, (ii) having at least one cysteine residue present from the recited zero to three cysteine residues of Domains I and IV, and (iii) self-assembling into particles on expression by a host cell wherein the particles so formed are substantially free of binding to nucleic acids and are more stable after storage at 37.degree. C. in a 20 mM sodium phosphate buffer at pH 6.8 for a time period of one month than are particles formed from otherwise identical HBc chimer molecules that contain both cysteine residues at positions 48 and 107.

Zlotnick teaches recombinant hepatitis B virus core (HBc) protein chimer molecule that has a length of about 135 to about 365 amino acid residues and contains four peptide-linked amino acid residue sequence domains from the N-terminus that are denominated Domains I, II, III and IV, wherein Domain I comprises about 72 to about 150 amino acid residues whose sequence includes: (i) at least the sequence of the residues of position 4 through position 75 of HBc, (ii) the substitution of another residue for the cysteine residue at position 48, (iii) zero cysteine residues at an amino acid position of the chimer molecule corresponding to amino acid position -20 to about +1 from the N-terminus of the HBc sequence of SEQ ID NO:1 [N-terminal cysteine residue(s)] in a sequence other than that of the HBc precore sequence, and (iv) *does not contain the* optional immunogenic epitope sequence containing up to about 75 amino acid residues peptide-bonded to one of HBc residues 2-4; Domain II comprises up to about 85 amino acid residues peptide-bonded to HBc residue 75 of Domain I in which (ii) the sequence of HBc at positions 76 through 85 is present and free from deletions or added heterologous residues; Domain III comprises an HBc sequence from position 86 through position 135 peptide-bonded to residue 85 of Domain II in which another residue is substituted for the cysteine of position 107; Domain IV comprises: (i) *fifteen* residues of an HBc amino acid residue sequence from position 136 through about 165 peptide-bonded to the residue of position 135 of Domain III, (ii) *one* cysteine residue(s) [C-terminal cysteine residue(s)] within about 30 residues from the C-terminus of the chimer molecule, (iii) zero ... amino acid residues in a sequence other than that present in HBc from position 165 to the C-terminus, and the sequence of the

chimer molecule from HBc position 150 through the C-terminus of the chimer molecule containing fewer than about ten arginine, lysine residues or mixtures of both residues; said chimer molecule (i) having an amino acid residue sequence in which up to about 10 percent of the amino acid residues are substituted in the HBc sequence of the chimer, (ii) having at least one cysteine residue present from the recited zero to three cysteine residues of Domains I and IV, and (iii) self-assembling into particles on expression by a host cell wherein the particles so formed are substantially free of binding to nucleic acids and are more stable after storage at 37.degree. C. in a 20 mM sodium phosphate buffer at pH 6.8 for a time period of one month than are particles formed from otherwise identical HBc chimer molecules that contain both cysteine residues at positions 48 and 107. As Zlotnick's core particle has the identical structure to that which Applicant claims, including the deletion of cysteine residues at positions 48 and 107, it is asserted that it has all of the properties inherent in such a molecule including the added stability at 37 degrees Celsius over a period of storage. (See also Zlotnick at page 9558, column 1).

Claims 25, 27-28, 30, 32 and 43-46 are rejected under 35 U.S.C. 102(a) as being anticipated by Jegerlehner et al.

Jegerlehner teaches recombinant hepatitis B virus core (HBc) protein chimer molecule that has a length of about 135 to about 365 amino acid residues and contains four peptide-linked amino acid residue sequence domains from the N-terminus that are

denominated Domains I, II, III and IV, wherein Domain I comprises about 72 to about 150 amino acid residues whose sequence includes: (i) at least the sequence of the residues of position 4 through position 75 of HBc, (ii) the substitution of another residue for the cysteine residue at position 48, (iii) zero ... cysteine residues at an amino acid position of the chimer molecule corresponding to amino acid position -20 to about +1 from the N-terminus of the HBc sequence of SEQ ID NO:1 [N-terminal cysteine residue(s)] in a sequence other than that of the HBc precore sequence, and (iv) *does not contain* the optional immunogenic epitope sequence containing up to about 75 amino acid residues peptide-bonded to one of HBc residues 2-4; Domain II comprises up to about 85 amino acid residues peptide-bonded to HBc residue 75 of Domain I in which (i) zero to all residues in the sequence of HBc positions 76 through 85 are present or replaced and peptide-bonded to one to about 75 amino acid residues that are heterologous to the HBc loop and constitute an immunogen, or a sequence of one to about 40 amino acid residues that constitute an anti-antigen or a chemically-reactive linker residue for a conjugated hapten ...; Domain III comprises an HBc sequence from position 86 through position 135 peptide-bonded to residue 85 of Domain II in which another residue is substituted for the cysteine of position 107; Domain IV comprises: (i) five through about thirty residues of an HBc amino acid residue sequence from position 136 through about 165 peptide-bonded to the residue of position 135 of Domain III, (ii) zero ... cysteine residues [C-terminal cysteine residue(s)] within about 30 residues from the C-terminus of the chimer molecule, (iii) zero ... amino acid residues in a sequence other than that present in HBc from position 165 to the C-terminus, and the sequence of

the chimer molecule from HBc position 150 through the C-terminus of the chimer molecule containing fewer than about ten arginine, lysine residues or mixtures of both residues; said chimer molecule (i) having an amino acid residue sequence in which up to about 10 percent of the amino acid residues are substituted in the HBc sequence of the chimer, (ii) having at least one cysteine residue present from the recited zero to three cysteine residues of Domains I and IV, and (iii) self-assembling into particles on expression by a host cell wherein the particles so formed are substantially free of binding to nucleic acids and are more stable after storage at 37.degree. C. in a 20 mM sodium phosphate buffer at pH 6.8 for a time period of one month than are particles formed from otherwise identical HBc chimer molecules that contain both cysteine residues at positions 48 and 107.

***Claim Rejections - 35 USC § 103***

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 2, 4-6, 16-22, 30-39 and 43-46 are rejected under 35 U.S.C. 103(a) as being unpatentable over Zlotnick, et al. (1997) as applied to claims 1, 3, 8-14, 23-28, 40-42 and 46 above, and further in view of Pumpens et al. (1995)

Pumpens et al. (1995) teaches immunogenic compositions and vaccines using recombinant HBc chimer molecules of a variety of lengths up to about 600 amino acid

residues in length. The chimers can carry insertions at the N-terminal, C-terminal or at internal sites. (See tables 1 through 3) Pumpens teaches that the chimers can contain B-cell and T-cell epitopes. (See page 71) These chimers contain an HBC sequence of at least about 130 of the N-terminal 150 amino acid residues of the HBc molecule (See for instance Fig. 1, pg. 64) that include a peptide-bonded heterologous epitope (Table 1, page 66) or a heterologous linker residue for a conjugated epitope present in the HBC immunodominant loop (see page 69, col. 1, last paragraph). Pumpens discloses that HBc chimeras with c-terminal truncations are capable of self-assembly and do not bind or 'pack' nucleic acid. (page 67, col. 1).

Pumpens makes two critical points on page 67. First, Pumpens reports "capsids formed by C-terminally truncated HBc monomers are less stable than the corresponding full-length protein particles." Second, that "foreign insertions [at this site] are not only possible but also exert a stabilizing effect on chimeric HBCΔ derivatives..." Pumpens does not teach adding a c-terminal cysteine residue to achieve the stabilizing effect.

One of ordinary skill in the art would have been motivated to combine the teachings of Pumpens outlining this various uses of HBc as an epitope carrier with that of Zlotnick because it was well known that HBc chimeras with c-terminal deletions, while still capable of self-assembly, were less stable than their full-length counterparts and that by adding back amino acid residues to these c-terminal deletion one could achieve a more stable chimera, while Zlotnick teaches that the addition of a cysteine residue to an HBc c-terminal truncation results in enhanced stability. One of ordinary skill in the art would have expected achieve a more stable HBc chimera with a c-terminal truncation

by the addition of a cysteine residue because Zlotnick teaches that the addition of a cysteine to the c-terminal of an HBc molecule with a c-terminal truncation results in enhanced stability. Therefore the invention as a whole would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made.

Claims 7, 15 and 29 are rejected under 35 U.S.C. 103(a) as being unpatentable over Pumpens et al. (1995) in view of Zlotnick, et al. (1997) as applied to claims 1-6, 8-14, 16-28 above, and further in view of Nassal, M. et al. (1992).

Claims 7, 15, and 29 are directed at the addition of cysteine residues to position 76 and 82 of the HBc core molecule in a core molecule where the cysteine residues at positions 48 and 107 have been removed. As outlined above, Zlotnick teaches the removal of the cysteine residues at positions 48 and 107 in an HBc molecule with a truncation at the C-terminal with the addition of a C-terminal cysteine residue. Nassal teaches the significance of the three N-terminal cysteine residues of the core molecule. Nassal teaches that these residues are not required for the formation of the core particles but contribute to the stability of the overall structure via interchain and intrachain linkages. (see table 1, page 1022). Zheng, J. et al. (1992) performed similar studies on the disulfide bonding patterns of hepatitis B core particles.

One of ordinary skill in the art would have been motivated to combine the teachings of Nassal, M et al. with those of Zlotnick and Pumpens because Nassal teaches that the stepwise addition of cysteine residues to an HBc molecule can be used to tailor the stability patterns of the resultant molecule. One of ordinary skill in the art

would have expected achieve a more stable HBc chimer by tailoring the particular cysteine resides within the molecule based upon the structural environments of the cysteine residues within the conformation of the overall HBc particle because Nassal teaches functions/effects of these residues within the core particle. Therefore the invention as a whole would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made.

Claims 2, 17, 30 and 31 are rejected under 35 U.S.C. 103(a) as being unpatentable over Zlotnick et al (1997) in view of Nierynck et al. (1998) Nature Medicine, 5(10):1157-1163.

Applicant claims a hepatitis B core molecule with a heterologous N-terminal sequence that constitutes an immunogen and/or an N-terminal cysteine residue.

Zlotnick et al. is as outlined above.

Neirynck teaches an HBc chimer molecule displaying the immunogenic M2 epitope from influenza virus at the N-terminal end of the chimer molecule. Neirynck utilized a full-length HBc core molecule, which would contain the C-terminal sequence, known to pack nucleic acid in the recombinant particles. The particle created by Neirynck had two N-terminal cysteine residues. (See fig. 1)

One of ordinary skill in the art would have been motivated to combine the teachings of Zlotnick with those of Neirynck because Zlotnick teaches the production of more stable hepatitis B core particles via addition of C-terminal cysteine with concomitant removal of internal cysteine residues and Zlotnick also teaches the removal

of the C-terminal protamine region, known to bind and pack endogenous nucleic acid, while Neirynck teaches that a universal vaccine may be created for influenza virus by the addition of the influenza M2 protein to the HBc core molecule sequence at the N-terminal end of the molecule. One of ordinary skill in the art would have expected an immunogenic HBc molecule with enhanced stability because the techniques were well known at the time of applicant's invention and are described in detail in the cited references. Therefore the invention as a whole would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made.

Claims 1-6, 8-14, 16-24, 26, 31, 33-42 rejected under 35 U.S.C. 103(a) as being unpatentable over Jegerlehner et al. as applied to claims 25, 27-28, 30, 32 and 43-46 above, and further in view of WO 01/98333 A2 to Page, et al.

WO 01/98333 A2 teaches modified hepatitis B core antigen where one or more of the four arginine repeats responsible for RNA binding have been deleted followed by the addition/retention of a C-terminal cysteine residue. WO 01/98333 A2 teaches "[t]he removal of the arginine repeats residues the binding of nucleic acid, whilst retention of the C-terminal cysteine allows for the formation of a stable particle." (See page 2) WO 01/98333 A2 teaches the addition of epitopes at the C-terminus, in and around the e1 loop from roughly residues 68 to 90 (i.e. the immunodominant loop) and the N-terminus. (See page 10) The epitopes may be B-cell epitopes or T-cell epitopes. (See page 11) The recombinant core antigen may contain multiple heterologous epitopes. (See page

11) Moreover, these epitopes may different epitopes from the same organism or even multiple copies of the same epitope within the core molecule. Epitopes may be conformational or linear. Epitopes may range widely in size, which would correspondingly affect the overall size of the chimer. WO 01/98333 A2 teaches that the protein self-assembles into particles which may closely resemble the particles formed by native HbcAg. (See page 9).

WO 01/98333 A2 teaches molecules that would satisfy the limitations of insert size as found throughout the claims, including but not limited to claims such as claims 2 or 6. WO 01/98333 A2 teaches molecules that would satisfy the limitations as to size of the resultant molecule as found throughout the claims, including but not limited to claims such as claim 9. WO 01/98333 A2 teaches molecules that would satisfy the limitations as to size and various permutations of the resultant HBc chimer sequence in the molecule as found throughout the claims, including but not limited to claims such as claim 10. As to claims 23-24, note that residues 48 and 107 are deleted in Jegerlehner.

One of ordinary skill in the art would have been motivated to add the teachings of WO 01/98333 A2 to the teachings of Jegerlehner et al. because WO 01/98333 A2 teaches that HBc core molecules as epitope carriers may be made more stable by the addition of C-terminal cysteines while also teaching the availability of numerous sites into which heterologous epitopes may be inserted. One of ordinary skill in the art would have expected to achieve a more stable HBc core molecule as an epitope carrier as the techniques were well-known at the time of Applicant's invention as evidenced by the various references cited in the present action including Pumpens et al. (1995), Zlotnick

et al., Gallina, et al. etc. Therefore the invention as a whole would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made.

***Double Patenting***

Claims 1-46 are provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable (1) over claims 1-78 of copending Application No. 09/930,915, (2) over claims 1-33 of copending Application No. 10/274,616, (3) over claims 1-53 of copending Application No. 10/787,734, (4) over claims 98-109 of copending Application No. 10/805,913 and (5) over claims 79-115 of copending Application No. 10/806,006. Although the conflicting claims are not identical, they are not patentably distinct from each other because instant claims 1-69 are drawn to the same subject matter, e.g., recombinant chimer HBC protein molecules that have C-terminal cysteines, self-assemble into particles, and have improved particle stability, as are claims 1-46 of 10/732,862, differing only in scope.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

***Conclusion***

Claims 1-46 are rejected.

The prior art made of record and not relied upon is considered pertinent to applicant's disclosure:

Conway, J.F. et al. Hepatitis B virus capsid: Localization of the putative immunodominant loop (residues 78 to 83) on the capsid surface, and implications for the distinction between c and e-antigens (1998) J. Mol. Biol. 279: 1111-1121.

Koschel, M. et al., Extensive mutagenesis of the hepatitis B virus core gene and mapping of mutation that allow capsid formation (1999) Journal of Virology, 73(3): 2153-2160.

Kratz, P. A. et al. Native display of complete foreign protein domains on the surface of hepatitis B virus capsids (1999) Proc. Natl. Acad. Sci., Vol. 96: 1915-1920.

Nassal, M. et al. An intramolecular disulfide bridge between cysteine-7 and cysteine61 determines the structure of the secretory core gene product (e antigen) of hepatitis B virus (1993) Journal of Virology, 67(7):4307-4315.

Pumpens, P. et al. Hepatitis core particles as a universal display model : a structure-function basis for development (1999) FEBS Letters, vol. 442:1-6. Pumpens teaches the various insertion sites into which an antigen may be added. Pumpens teaches that "although C-terminally truncated HBc monomers are less stable than the corresponding full-length protein particles, foreign insertions are not only possible, but also exert a stabilizing effect on chimeric HBc deletion derivatives." See page 67, col. 1.

Pumpens, P. et al. HBV core particle as a carrier for B cell/T cell epitopes (2001) Intervirology, 44: 98-114.

Schodel, F. et al. Structure of hepatitis B virus core and e-antigen (1992) The Journal of Biological Chemistry, 268(2):1332-1337.

Seifer, M. et al. Stability governs the apparent expression of "particulate" hepatitis B e antigen by mutant hepatitis B virus core particles (1993) Virology 196:70-78.

Watts, N. R. et al. The mophogenic linker peptide of HBV capsid protein forms a mobile array of the interior surface (2002) EMBO Journal, Vol. 21, No. 5, pp. 876-884.

Ulrich, R. et al. Core particles of hepatitis B virus as carrier for foreign epitopes (1998) Advances in Virus Research, vol. 50:141-182.

Zheng, J. et al. The structure of hepadnaviral core antigens (1992) The Journal of Biological Chemistry, 267(13):9422-9429.

Zhou, S. et al. Cysteine residues of the hepatitis B virus capsid protein are not essential for the assembly of viral core particles but can influence their stability (1992A) Journal of Virology, 66(9): 5393-5398.

Zhou, S. et al. Hepatitis B virus capsid particles are assembled from core protein dimer precursors (1992B) Proc. Natl. Acad. Sci. 89:10046-10050.

Zhou, S. et al. Charaterization of hepatitis B virus capsid particle assembly in Xenopus oocytes (1992C) Journal of Virology, 66 : 3086-3092.

Zlotnick, et al., Dimorphism of hepatitis B virus capsids in strongly influenced by the C-terminus of the capsid protein (1996) Biochemistry, 35:7412-7421.

Gallina, A. et al A recombinant hepatitis B core antigen polypeptide with the protamine-like domain deleted self-assembles into capsid particles but fails to bind nucleic acids (1989) Journal of Virology, 63(11): 4645-4652. The teachings of Gallina et al (1989) predate the teachings of Zlotnick, also teaching C-terminal cysteine residues.

Gallina teaches a hepatitis B core molecule that ends at residue 144 and has a six amino acid carboxy-terminal tail with two cysteine residues. (See page 4647, col. 1)

See also Form 892 for references cited.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Michael M. McGaw whose telephone number is (571) 272-2902. The examiner can normally be reached on Monday through Friday from 8 A.M. to 5 P.M..

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, James Housel can be reached on (571) 272-0902. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

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M.M.

Friday, December 03, 2004

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